PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	03 OCT 2005
FOR FURTHER ACTION	See paragraph 2 below

Applicant's or agent's file reference		
96700/950		
International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/07365	07 March 2005 (07.03.2005)	11 March 2004 (11.03.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/70; A01N 43/04; C07G 11/00 and US Cl.: 514/44; 536/4.1, 16.8

Applicant

ALBERT EINSTEIN COLLEGE OF MEDICINE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Jennifer Dunston Telephone No. 571-272-0507

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US05/07365

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search..

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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International application No.
PCT/US05/07365

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-38	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-38	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-38	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-38 the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the use of an agent effective to increase transcription of a gene in combination with an agent capable of increasing the production of the protein disrupted by a mutation in the same gene.

Claims 1-38 the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-38 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art. The claims are drawn to or encompass the treatment of any disease comprising administering an agent effective to increase the transcription of a gene disrupted by a genetic mutation in combination with an agent that allows a functional protein to be expressed from the defective gene. Further, the claims are drawn to or encompass the administration to a subject an agent that activates a promoter of a gene disrupted by a mutation. The nature of the invention is complex in that the agents must act on the gene disrupted by a mutation. Further, the claims are drawn to or encompass the treatment of a genetic disease using the abovementioned method. The breadth of the claims further exacerbates the complexity of the invention. The specification teaches that ofloxacin and thioguanine are capable of increasing transcription from an atm promoter in an *in vitro* assay (e.g. paragraphs [0029]-[0040]; Table 2). The specification does not teach how to use ofloxacin and thioguanine to increase the expression of any gene that may be disrupted by a mutation. The specification teaches that agents may be identified using *in vitro* promoter assays. However, the use of *in vitro* cultures to model human disease can be unpredictable. For example, Stamatoyannopoulos teaches that compounds that induce fetal hemoglobin expression in patients do not induce fetal hemoglobin expression in clonal cultures when they are well controlled for maturation (e.g. page 262, left column, last paragraph). Thus, the results of an *in vitro* assay are not necessarily predictive of the effect in a subject. Furthermore, the use of nucleic acid molecules to correct a defect caused by a genetic mutation was underdeveloped and unpredictable at the time the invention was made. Parakh-Olmedo et al teach that oligonucleotide delivery must be optimized before gene repair is considered useful for clinical applications and that animal models must be tested to validate the overall approach (e.g. page 639, In brief). In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention.